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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SANDALS, WILLIAM O

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/957,456	Underhill et al.
Examiner	**Art Unit**
William Sandals	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 22, 2003*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above, claim(s) *14-26* is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Sep 21, 2001* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group I, claims 1-13 in Paper No. 7, filed January 22, 2003 is acknowledged.

2. Claims 14-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Groups II-VI, claims 14-26, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 7.

Drawings

3. New formal drawings are required in this application because recent changes to the MPEP, section 608.02(c) no longer allow deferral of submission of drawings pursuant to notification. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the Patent and Trademark Office no longer prepares new drawings. See the attached Notice of Draftsman's Review.

Specification

4. The disclosure is objected to because of the following informalities: In the Brief Description of the Drawings, at page 5, there is no description of figure 5B.

Appropriate correction is required.

Claim Objections

5. Claim 4 is objected to because of the following informalities: Claim 4 recites at lines 1-2 "wherein the reporter gene encodes an enhancer element", since the enhancer element is in the non-transcribed, non-translated region upstream of the encoded portion of the gene. Since the gene does not "encode" an enhancer, but rather is "operably linked to" an enhancer , amending the claim to recite "wherein the reporter gene is operably linked to an enhancer element" would cure this defect. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. When biological material is required to practice an invention, and if it is not so obtainable or available, the enablement requirements of 35 USC §112, first paragraph, may be satisfied by a deposit of the material. See 37 CFR 1.802.

The specification lacks complete deposit information for the deposit of the plasmid "pGL3(4X48)-enhanced green fluorescent protein". Because it does not appear that the plasmid

"pGL3(4X48)-enhanced green fluorescent protein" is known and publicly available or can be reproducibly isolated from nature without undue experimentation, a suitable deposit for patent purposes is required.

Applicant's have not indicated the deposit of the plasmid "pGL3(4X48)-enhanced green fluorescent protein" in the claims or specification. Therefore, there is an insufficient assurance that a required deposit has been made and all the conditions of M.P.E.P. 608.01(p)(C) are met because:

a- If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that **the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements.** See 37 CFR 1.808, and,

For each deposit made pursuant to these regulations, the specification shall contain:

(1) The accession number for the deposit;
(2) The date of the deposit;
(3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and
(4) The name and address of the depository. See 37 CFR 1.809(d).

-or-

b- If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or Declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification. In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements, and,

For each deposit made pursuant to these regulations, the specification shall contain:

(1) The accession number for the deposit;

(2) The date of the deposit;

(3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and

(4) The name and address of the depository. See 37 CFR 1.809(d).

7. Amendment of the specification to conform to either a- or b- above is required.

8. Claims 8 and 9 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth above.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1 (and dependent claims 2-13) and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 1 is drawn to a method of identifying a modulator of chondrogenesis. Step (a) provides cells which can differentiate into chondroblasts or chondrocytes. Step (b) requires the transfection of the cells. Step (c) recites adding a test compound to the transfected cells. Step (d) recites determining the effect of the test compound on cell differentiation. Step (d) does not relate to the preamble of the claim for identifying a modulator of chondrogenesis. Additionally, there is no nexus between step (b) and step (d), since the "determining" of step (d) does not require that the transfection of the cells in step (b) be related to the determining of differentiation, nor to the detection of differentiation in step (d), (ie., there is no relation of the reporter gene expression to differentiation). The claim is therefore vague and indefinite.

12. Claim 8 recites that "the marker encodes a luciferase or enhanced green fluorescent protein". Claim 8 depends from claim 6. Claim 6 recites that "the nucleic acid construct comprises at least one Sox9 binding site, a promoter and a detectable marker" (the "marker" of dependent claim 8 above). Claim 6 depends from claim 5 which depends from claim 4. Claim 4 recites that "the reporter gene encodes an enhancer element that binds to a transcription factor". Claim 4 depends from claim 1. Claim 1 recites at section (b), "a nucleic acid construct comprising a reporter gene" (the "reporter gene" of dependent claim 4). The "marker" of claim 8 therefore is comprised in the nucleic acid of claim 1, section (b) but the "marker" of claim 8 is not the "reporter gene" of claims 1 and 4, since the marker genes of claim 8 (luciferase or Green fluorescent protein) are not "enhancer elements". It is not clear why the "marker" of claim 8 is present in the construct, since the "reporter gene" of claim 1 is claimed as the "enhancer

element" of claim 4. The logic of a "nucleic acid construct" which comprises a "reporter gene" which encodes an "enhancer element", but where the "reporter gene" does not encode the "marker gene" (luciferase or Green fluorescent protein of dependent claim 8) does not easily follow. It would be expected that the reporter gene of claim 1 would be the luciferase or the Green fluorescent protein of dependent claim 8. Since this cannot be the case, it is not clear how the luciferase or the Green fluorescent protein may operate as a marker gene in the construct.

If on the other hand, the claim is meant to include a marker gene in addition to the reporter gene, then claims 6 and 8 are unclear as to this meaning, and the claim should be amended to clarify the distinction between the reporter gene and the marker gene. The claims are therefore vague and indefinite.

Amending claim 6 to state "further comprising a marker gene" would clarify the relationship of the reporter gene to the marker gene.

13. Claim 9 is drawn to "wherein the nucleic acid construct is pGL3(4X48)-luciferase". Claim 9 depends from claim 6. Claim 6 depends from claim 4 which recites that the "reporter gene" is an "enhancer element". As noted in the rejection of claim 8 above, the "the nucleic acid construct is pGL3(4X48)-luciferase" of claim 9, is not the "enhancer element" of claim 4. There is a logical disconnect between "the nucleic acid construct comprising the reporter gene" of claim 1 (the "reporter gene" is the "enhancer element" of claim 4) and "the nucleic acid construct is pGL3(4X48)-luciferase" of claim 9.

If on the other hand, the claim is meant to include a marker gene in addition to the reporter gene, then claims 6 and 9 are unclear as to this meaning, and the claim should be amended to clarify the distinction between the reporter gene and the marker gene. The claims are therefore vague and indefinite. Therefore, the meaning of claim 9 is vague and indefinite.

Amending claim 6 to state "further comprising a marker gene" would clarify the relationship of the reporter gene to the marker gene. Additionally, since the pGL3(4X48)-luciferase plasmid contains the enhancer region of Col2A1, it would appear that the language of claim 9 is better understood if it depends from claim 1, not from claim 6. A further clarification of the pGL3(4X48)-luciferase plasmid construction in the language of claim 9 would also be helpful to relate the functional domains of the plasmid as they relate to the functional domains recited in base claim 1.

14. Claim 10 is drawn to "wherein the nucleic acid construct is pGL3(4X48)-luciferase". Claim 10 depends from claim 6. Claim 6 depends from claim 4 which recites that the "reporter gene" is an "enhancer element". As noted in the rejection of claim 8 above, the "the nucleic acid construct is pGL3(4X48)-luciferase" of claim 10, is not the "enhancer element" of claim 4. There is a logical disconnect between "the nucleic acid construct comprising the reporter gene" of claim 1 (the "reporter gene" is the "enhancer element" of claim 4) and "the nucleic acid construct is pGL3(4X48)-luciferase" of claim 10.

If on the other hand, the claim is meant to include a marker gene in addition to the reporter gene, then claims 6 and 10 are unclear as to this meaning, and the claim should be

amended to clarify the distinction between the reporter gene and the marker gene. The claims are therefore vague and indefinite. Therefore, the meaning of claim 10 is vague and indefinite.

Amending claim 6 to state "further comprising a marker gene" would clarify the relationship of the reporter gene to the marker gene. Additionally, since the pGL3(4X48)-luciferase plasmid contains the enhancer region of Col2A1, it would appear that the language of claim 10 is better understood if it depends from claim 1, not from claim 6. A further clarification of the pGL3(4X48)-luciferase plasmid construction in the language of claim 10 would also be helpful to relate the functional domains of the plasmid as they relate to the functional domains recited in base claim 1.

15. The term "at high density" in claim 12 is a relative term which renders the claim indefinite. The term "at high density" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The prior art does not provide a standard for the density of cells in a plate, since a few cells per unit of surface area may be a "high density" a particular cell type, where several hundred cells per unit of surface area may be a "high density" a different cell type. There being no art recognized standard, the claims are therefore vague and indefinite.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1, 2, 4-8, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by LeFebvre et al. (Matrix Biol.).

LeFebvre et al. teach at the abstract, page 530 at the section entitled "SOX9 Is a Typical Transcription Factor", page 534, page 535, column 2 bottom to page 536 column 1, and figure 4, a method of identifying a modulator of chondrogenesis by transiently transfecting cells of mesenchymal origin capable of differentiating into chondroblasts or chondrocytes (see page 533, column 1 bridging to the middle of column 2 and page 535, column 1 bridging to the middle of column 2) with a plasmid encoding Col2A1 enhancer elements linked to a *luc* reporter (the construct comprising a reporter gene), and cotransfecting the cells with a plasmid encoding Sox9 (the "test compound", see LeFebvre et al. at figure 4). The Sox9 protein expressed from the plasmid binds to the Col2A1 enhancer elements, inducing expression of the *luc* reporter. The pFlag marker is also used in the transfected cells.

18. Claims 1, 2, 4-8, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by LeFebvre et al. (EMBO J.).

LeFebvre et al. teach a method of identifying a modulator of chondrogenesis by transiently transfecting cells of mesenchymal origin capable of differentiating into chondroblasts or chondrocytes (see the abstract) with a plasmid encoding Col2A1 enhancer elements linked to a *luc* reporter (the construct comprising a reporter gene), and cotransfecting the cells with a plasmid encoding Sox9 (the "test compound", see page 5726, column 2 to page 5727). The Sox9 protein expressed from the plasmid binds to the Col2A1 enhancer elements, inducing expression of the *luc* reporter. The pFlag marker is also used in the transfected cells.

19. Claims 1, 2, 4 and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Nonaka et al.

Nonaka et al. teach at the abstract and page 800, a method of identifying a modulator of chondrogenesis by transiently transfecting cells of mesenchymal origin capable of differentiating into chondroblasts or chondrocytes (see the abstract and materials and methods) with a plasmid encoding Col2A1 enhancer elements linked to a *lacZ* reporter (the construct comprising a reporter gene), and cotransfecting the cells with a plasmid encoding Sox9 (the test compound, see Nonaka et al. at figure 8). The Sox9 protein expressed from the plasmid binds to the Col2A1 enhancer elements, inducing expression of the *lacZ* reporter.

20. Claims 1, 2, 4-6, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Xie et al.

Xie et al. teach at the abstract and pages 758 and 762, a method of identifying a modulator of chondrogenesis by transiently transfecting cells capable of differentiating into cells of mesenchymal origin (chondroblasts or chondrocytes) (see page 758, column 1) with a plasmid encoding Col2A1 enhancer elements linked to a *luc* reporter (the construct comprising a reporter gene), and cotransfecting the cells with a plasmid encoding Sox9 (the test compound, see Xie et al. materials and methods). The Sox9 protein expressed from the plasmid binds to the Col2A1 enhancer elements, inducing expression of the *luc* reporter.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 1-8 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of LeFebvre et al. (Matrix Biol.) or LeFebvre et al. (EMBO J.) in view of Healy et al.

The claims are drawn to a method of identifying a modulator of chondrogenesis by (transiently, as recited in claim 11) transfecting cells capable of differentiating into chondroblasts or chondrocytes (cells of mesenchymal origin as recited in claims 2-3) with a nucleic acid construct comprising a reporter gene. The reporter gene may encode an enhancer element linked to a reporter, as claimed in claim 4. The reporter gene may be responsive to the transcription

factor Sox9 (as recited in claim 5). The test compound may be a nucleic acid molecule comprising a test gene that is transfected into the cells (as recited in claim 13).

LeFebvre et al. (Matrix Biol.) teach at the abstract, page 530 at the section entitled "SOX9 Is a Typical Transcription Factor", page 534, page 535, column 2 bottom to page 536 column 1, and figure 4, a method of identifying a modulator of chondrogenesis by transiently transfecting cells of mesenchymal origin capable of differentiating into chondroblasts or chondrocytes (see page 533, column 1 bridging to the middle of column 2 and page 535, column 1 bridging to the middle of column 2) with a plasmid encoding Col2A1 enhancer elements linked to a *luc* reporter (the construct comprising a reporter gene), and cotransfecting the cells with a plasmid encoding Sox9 (the "test compound", see LeFebvre et al. at figure 4). The Sox9 protein expressed from the plasmid binds to the Col2A1 enhancer elements, inducing expression of the *luc* reporter. The pFlag marker is also used in the transfected cells.

LeFebvre et al. (EMBO J.) teach a method of identifying a modulator of chondrogenesis by transiently transfecting cells of mesenchymal origin capable of differentiating into chondroblasts or chondrocytes (see the abstract) with a plasmid encoding Col2A1 enhancer elements linked to a *luc* reporter (the construct comprising a reporter gene), and cotransfecting the cells with a plasmid encoding Sox9 (the "test compound", see page 5726, column 2 to page). The Sox9 protein expressed from the plasmid binds to the Col2A1 enhancer elements, inducing expression of the *luc* reporter. The pFlag marker is also used in the transfected cells.

Each of LeFebvre et al. (Matrix Biol.) or LeFebvre et al. (EMBO J.) do not teach the mesenchymal cells from a limb bud as recited in claim 3.

Healy et al. teach at the abstract, introduction and page 74 the expression of recombinant SOX9 in mesenchymal cells from a limb bud which induces the mesenchymal limb bud cells to differentiate into chondroblasts and chondrocytes.

One of ordinary skill in the art would have been motivated at the time of making the instant invention to modify the transient co-expression of SOX9 and Col2A1 in fetal mesenchymal cells from the rib of an embryonic rat of LeFebvre et al. (Matrix Biol. or EMBO J.) by substituting mesenchymal limb bud cells for the mesenchymal rib cells for the expected benefit that mesenchymal cells from the limb bud allow the direct assessment of the effects of SOX9 expression in skeletonogenic and chondrogenic tissues. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of LeFebvre et al. (Matrix Biol.), LeFebvre et al. (EMBO J.) and Healy et al. who demonstrate the expression of SOX9 in mesenchymal cells to investigate the effects of SOX9 expression on mesenchymal cell differentiation.

Conclusion

23. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or

applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Tech Center customer service center at telephone number (703) 308-0198.

William Sandals, Ph.D.
Examiner
April 10, 2003

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
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